NorCal SOT Fall Symposium

A Tale of Two Fields: Reproductive & Juvenile Toxicity, and Public Health & Risk Assessment

October 22, 2015

Venue: South San Francisco Conference Center, 255 South Airport Boulevard, South San Francisco, CA 94080

Morning Session: Developmental, Reproductive and Juvenile Toxicity in Drug Development	
7:30 am – 8:30 am	**Registration and Breakfast**
8:30 am – 8:45 am	**Opening message from The NorCal President** *Eric Harstad, PhD, DABT, Senior Scientist and Therapeutic Area Leader, Genentech Inc.*
8:45 am – 9:45 am	**Identifying toxicity in the adult reproductive system: important considerations for interpreting male and female specific endpoints** *Dianne Creasy,PhD, DipRCPath (Tox), FRCPath, Dianne Creasy Consulting LLC.*
9:45 am – 10:45 pm	**Current State and Future of Reproductive and Developmental Toxicity Testing** *Alan M. Hoberman, Ph.D., DABT, Fellow ATS, Executive Director of Global Developmental, Reproductive and Juvenile Toxicology, Charles River Laboratories*
10:45 am – 11:00 am	**Coffee Break**
11:00 am – 12:00 pm	**Juvenile Animal Studies to Support Pediatric Drug Development: How, why, what?** *LaRonda L. Morford, PhD., Senior Research Advisor, Toxicology, Eli Lilly and Company*
12:00 pm – 1:30 pm	**Lunch Break, Lunch with Experts**
Afternoon Session: Merging Public Health and Traditional Risk Assessment at Cal/EPA-George Alexeeff's Legacy	
1:30 pm – 1:45 pm	**Chapter announcements and acknowledgements**
1:45 pm – 2:45 pm	**CalEnviroScreen: A Tool for Evaluating California Communities** *John Faust, PhD, Chief of the Community Assessment and Research, OEHHA*
2:45 pm – 3:00 pm	**Coffee Break**
3:00 pm – 4:00 pm	**Approaches to Including Sensitive Subpopulations in Risk Assessment** *Melanie A. Marty, PhD, Acting Deputy Director for Scientific Affairs, OEHHA*
4:00 pm – 5:00 pm	**California's Public Health Goal for Perchlorate in Drinking Water** *Elaine Khan, PhD, Chief of the Water Toxicology Section, OEHHA*
5:00 pm – 5:15 pm	**Closing Remarks**
5:15 pm – 6:15 pm	**Reception and Networking**

DIRECTIONS TO SSF CONFERENCE CENTER

ABSTRACTS

Identifying toxicity in the adult reproductive system: important considerations for interpreting male and female specific endpoints

Dianne Creasy,PhD, DipRCPath (Tox), FRCPath, Dianne Creasy Consulting LLC.

Chemically induced disturbances in reproductive efficiency of adults can occur through a variety of mechanisms. Identification of reproductive toxicants in routine regulatory studies relies on the measurement and informed evaluation of a number of male- and female- specific reproductive endpoints. Many of the endpoints are inter-related but each provides unique information about the potential mechanism of toxicity. It is important to consider the overall correlations and patterns of changes in all endpoints to gain insight into toxicological mechanisms. For example, a test article-related reduction in caudal epididymal sperm count could occur due to reduced spermatogenesis in the seminiferous tubules, reduced viability of the sperm caused by reduced testosterone production, or reduced storage of the sperm in the epididymis caused by estrogenic stimulation. Evaluation of other endpoints such as organ weights, spermatid head counts and histopathological findings are essential in distinguishing between these potential mechanisms, but it is important to know how the various endpoints inter-relate with one another. Most male mediated reproductive toxicity involves non-hormonal mechanisms of spermatogenic disturbances in the testis. Histopathological evaluation of the testes is considered a very sensitive endpoint for detecting spermatogenic disturbances, but this is only true if the tissue is fixed optimally and the pathologist is trained in “stage aware evaluation”. In addition, some mechanisms of male reproductive toxicity that result in altered sperm parameters or reduced fertility, will not involve any histopathologic changes, so absence of histopathologic changes should not necessarily be used as a major reason to discount changes in sperm parameters. In contrast to the male, reproductive toxicity in the female most commonly involves hormonal disturbances. The hormonal disturbance may be the primary cause of the toxicity or may be a secondary response to the toxicity, but the histopathologic changes in the reproductive tissues and physiological changes in estrous cyclicity (monitored by vaginal smears) provide the most important clues for mechanistic information. Confounding factors such as stress and reduced body weight will affect some of the measured endpoints in both males and females, but it is important to know which endpoints are sensitive to stress and which are not, so that test article related changes are not missed. This talk will discuss the utility and sensitivity of the various reproductive endpoints monitored in regulatory studies, how they inter-relate, and will also provide some important considerations that need to be appreciated when interpreting changes.

Current State of and Future of Reproductive and Developmental Toxicity Testing

Alan M. Hoberman, Ph.D., DABT, Fellow ATS, Executive Director, Global Developmental, Reproductive and Juvenile Toxicology, Charles River Laboratories.

It has been over 20 years since the promulgation of the ICH S5 guideline for reproduction and developmental toxicity testing. Over this time, the introduction of biologics has moved the NHP model from a third species after the rat and rabbit, to a primary species for testing. Various other new DART models including, other rodents, transgenic animals with and without surrogate molecule exposure, non-mammalian species and in –vitro assays have been used to move drugs to approval, without ever being mentioned in the ICH S5 guidance. Other ICH documents (ICH M3) have modified the timing of when we test and still other (ICH 9) guidance modifies the amount of DART testing we conduct for some classes of drugs. All of these issues and the overall utility of rat and rabbit studies are being considered in the revisions to the ICH S5 guidance currently being discussed. This presentation will focus on the current state of DART and review impending changes.

Juvenile Animal Studies to Support Pediatric Drug Development: How, why, what?

LaRonda L. Morford, PhD., Senior Research Advisor, Toxicology, Eli Lilly and Company.

Consideration of if and when juvenile animal studies (JAS) are needed to support the clinical development of pharmaceuticals is now an important part of drug development. Unlike the highly defined study designs of the standard core of toxicity studies conducted to support registration, the need for and

design of juvenile toxicity studies are intended to be driven on a case-by-case basis. While the number of JAS conducted continues to increase, the "how's", "why's" and "what's" of nonclinical testing strategies are still evolving. This talk will address regulatory requirements and guidelines related to pediatric drug development, potential nonclinical strategies to support pediatric drug development and general design considerations of JAS, with both small molecules and biopharmaceuticals. The value of JAS and challenges related to supporting pediatric safety will be highlighted.

CalEnviroScreen: A Tool for Evaluating California Communities

John Faust, PhD, Chief of the Community Assessment and Research, OEHHA

Many Californians are burdened by multiple sources of pollution and some people are more vulnerable to these exposures. We developed a tool, called CalEnviroScreen, which uses existing environmental, health, and socioeconomic data to create a cumulative impacts score for different geographic areas across California. We conducted a statewide screen at the census tract scale to identify communities most burdened by multiple sources of pollution with populations that may be especially vulnerable to its effects. The method develops the concept of cumulative impact based on a suite of indicators of exposure, environmental conditions, sensitive populations, and socioeconomic factors. The screen uses data for ambient ozone and PM2.5 concentrations, diesel PM, traffic density, toxic releases from facilities, pesticide use, cleanup sites, impaired waters, groundwater threats, solid and hazard waste facilities, low birth weight infants, asthma, prevalence of children and elderly, educational attainment, linguistic isolation, poverty, and unemployment. The analysis consists of a relative comparison of approximately 8000 census tracts in California. The comparisons can be viewed by individual indicators, or by measures of pollution burden or measures of vulnerability. The results are available through a GIS mapping interface.

Approaches to Including Sensitive Subpopulations in Risk Assessment

Melanie A. Marty, PhD, Acting Deputy Director for Scientific Affairs, OEHHA

Traditional cancer risk assessment approaches for environmental chemicals have relied on epidemiological studies primarily in occupationally-exposed individuals or on animal cancer bioassays that begin around sexual maturity. In both cases, exposures in utero and postnatally are not included. Similarly, much of the risk assessment for non-cancer endpoints has relied on animal experiments where exposures start after maturity, and rarely human exposures primarily in adults. Further, differences in response to toxicants among humans is not typically readily quantifiable for most environmental toxicants. In addition, a developing body of evidence is evaluating the complex interactions of non-chemical stressors and chemicals toxicants. This presentation will walk through some of the risk assessment approaches CalEPA's Office of Environmental Health Hazard Assessment is using to include evidence of variability in toxic response by age at exposure and by genetic variability. The presentation will also include needs for approaches around interactions of non-chemical stressors and environmental toxicants.

California's Public Health Goal for Perchlorate in Drinking Water

Elaine Khan, PhD, Chief of the Water Toxicology Section, OEHHA

In 2004, the Office of Environmental Health Hazard Assessment (OEHHA) established a Public Health Goal (PHG) of 6 parts per billion (ppb) for perchlorate in drinking water. A PHG is the level of a chemical contaminant in drinking water that does not pose a significant risk to health. PHGs are not regulatory standards but state law requires that drinking water standards or Maximum Contaminant Levels (MCLs) be set as close to the corresponding PHG as technologically and economically feasible. Perchlorate is currently not regulated at the federal level but publication of the PHG in 2004 led to the establishment of the California MCL of 6 ppb in 2007. The PHG was based on the inhibition of thyroidal iodide uptake, which can lead to decreased thyroid hormone production. Potential impacts of decreased thyroid hormones include goiter, cretinism, cardiovascular disease, changes in lipid metabolism, and developmental and cognitive effects in the fetus and infants. OEHHA has since reviewed and updated the perchlorate PHG, lowering the value from 6 ppb to 1 ppb in 2015. While the critical effect and critical

study were retained, the updated PHG took into account recent data on the susceptibility of the fetus and infants to small changes in thyroid hormones. Thus, the 2015 PHG identified infants as a sensitive subpopulation and accordingly applied an updated uncertainty factor, relative source contribution, and drinking water intake rate.

BIOGRAPHIES

Dianne Creasy, PhD, DipRCPath (Tox), FRCPath, is a Toxicological Pathologist who has worked in regulatory toxicology for over 30 years. She has worked in the pharmaceutical and chemical industries as well as in academic research and contract research laboratories. She gained her PhD from University College, London with a thesis on mechanisms of chemically induced testicular toxicity and became Board Certified in Toxicological Pathology from the Royal College of Pathologists in London. Dianne has been working in the US, for Huntingdon Life Sciences since 1999, initially as a study pathologist and then Director of the Pathology department and more recently as Senior Scientific Advisor and Consultant Pathologist. She now provides an independent consultancy service in toxicologic pathology through her own company. Dianne has published widely on reproductve toxicity, particularly in the male, and has given many workshops and seminars on the practical aspects of evaluating the male and female reproductive tracts for toxicity.

Alan M. Hoberman, PhD, DABT, Fellow ATS, worked in the field of toxicology for over 40 years and has specialized in reproductive and developmental toxicology for over 35 years. As a Diplomat of the American Board of Toxicology (since 1988) and a Fellow of the Academy of Toxicological Society (since 2006), he has over 85 publications and over 200 presentations of abstracts and lectures in the fields of reproductive and developmental toxicology, neuro-toxicology, inhalation toxicology, photobiology and regulatory toxicology. His current research interests include the development of the immune response and the assessment of compounds in young animals.

Dr. Hoberman trained in anatomy and embryology at the University of Virginia and in toxicology at the University of Arkansas and the National Center for Toxicological Research. He was Head of the Reproductive Toxicology and Genetic Toxicology Section of Hazleton Laboratories, America, in Vienna, Virginia, for two years prior to joining Argus Research Laboratories, now Charles River Laboratories, Horsham PA. USA.

Additionally, Dr. Hoberman is a former President of the Middle Atlantic Reproduction and Teratology Association and former President of the Reproductive and Developmental Toxicology Specialty Section (2011). He presented a course on interpretation of data from reproductive toxicity evaluations held at the International Federation of Teratology Societies meeting in Boca Ratan, Florida, in 1991. He was President of the Arkansas Biotechnology Association from 1999-2000. He is currently the treasurer of the American College of Toxicology and the Pennsylvania Society for Biomedical Research, where is also a board member.

Currently Dr. Hoberman is responsible for designing, supervising and evaluating reproductive and developmental, reproductive and juvenile toxicity studies throughout Charles River. He manages the budget and personnel projections and long-term strategic plans for Charles River in these specialty areas. His level of expertise in all aspects of preclinical toxicology and chemical safety testing has proven invaluable in integrating our specialization areas into the overall approval process to bring new entities to market. In 2012, he co-edited and published a book on Pediatric Testing.

LaRonda L Morford, PhD, has over 15 years of industry experience working in toxicology including numerous presentations and publications related to juvenile animal studies. She is currently a Senior Research Advisor at Lilly responsible for nonclinical safety assessments of small molecule and biopharmaceutical programs from discovery through post-marketing. Dr. Morford is also Lilly's subject matter expert on nonclinical support of pediatric drug development where she is responsible for the high-level oversight of the nonclinical strategies and juvenile animal studies. Prior to Lilly, Dr. Morford was the Director of Juvenile Toxicology at WIL Research Laboratories where she was responsible for the scientific functions within Juvenile Toxicology and Neuroscience. Dr. Morford received her B.A. from Thomas More College in Crestview Hills, Kentucky and her Ph.D. from the University of Cincinnati in Cincinnati, OH.

John Faust, PhD, is a senior toxicologist in the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment in Oakland, California. Dr. Faust has managed the development of the California Communities Environmental Health Screening Tool (CalEnviroScreen) as a way to consider the combined burden of environmental pollutants in decision-making. This work has included evaluating scientific data on health and exposure disparities, population vulnerability, especially in low-income or minority populations.
Dr. Faust has also provided technical expertise to the office in the areas of toxicology, carcinogenic mode of action, dose-response assessment, and risk assessment. Other work has involved identification of new carcinogenic hazards, establishing cancer potencies and standards for contaminants in drinking water. He received his bachelor's degree in Biochemistry from Virginia Tech and his Ph.D. from Duke University in Pharmacology and Toxicology.

Melanie Marty, PhD, was appointed Acting Deputy Director for the Science Division at May, 2015. In this capacity, Dr. Marty provides scientific technical review of documents from all the OEHHA programs prior to release, and oversees the scientific activities of the division. Dr. Marty has been at OEHHA for more than 28 years and previously served as Branch Chief of the Air Toxicology and Epidemiology Branch from 1998 to 2012, and as Assistant Deputy Director for the Science Division from 2012-2015. She has served on a number of EPA peer review committees and was the Chair of the U.S.EPA's Children's Health Protection Advisory Committee from 2001-2009. Dr. Marty is also an Adjunct Assistant Professor at the University of California, Davis, Department of Environmental Toxicology. Dr. Marty received her Ph.D. from the University of California, Davis in Pharmacology and Toxicology.

Elaine Khan, PhD, has a degree in Biochemistry and Molecular Biology from UC Davis: studied crosstalk between the aryl hydrocarbon receptor and other signaling pathways with Mike Denison. Postdoc at the Center for Comparative Respiratory Biology and Medicine at UC Davis: investigated epidermal growth factor receptor signaling and trafficking under cigarette smoke-induced oxidative stress with Tzipora Goldkorn. Joined OEHHA in 2008 as an Associate Toxicologist in the Air Toxicology and Epidemiology Branch. Became chief of the Water Toxicology Section, which oversees the development of public health goals, in 2011.